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Research Article

Could Antimicrobial-like Peptides Play Multifunctional Roles in the Course of Cancer Treatments and Therapies: A Review and Prospectus

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Abstract

The present report focuses on the use of antimicrobial-like (AMPL) amphipathic peptides as therapeutic agents in the course of treating human cancers. As an example of such an AMPL peptide, a 34 amino acid peptide has been isolated and synthesized from a tumor-associated full-length pregnancy protein, termed alpha-fetoprotein (AFP). This alpha fetoprotein derived peptide has been termed the "Growth Inhibitory Peptide" (GIP). Henceforth, this report will describe the characteristics of an AMPL peptide together with the origin, discovery, significance, and function of the AMPL-GIP. These studies have employed both in vivo and in vitro-based experiments using AMPL-GIP. Following an initial discussion of AMPL peptides, the mechanism of cell penetration and tumor growth/suppression by such peptides via the cell growth cycle is described. Additional biological activities, toxicities, and side effects of GIP as a potential therapeutic peptides agent are further addressed. Overall, the topics covered in the present report discuss the discovery, isolation, purification, and assay developments of an AMPL-peptide while describing the advantages of the multiple biologic activities exhibited by this AMPL-growth inhibitory peptide.

Keywords

Alpha-fetoprotein, Peptides, Growth, Cell cycle, Cell targeting, Chromosome instability, Metastasis, Cancers, Fetuses.

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Introduction

A) Characteristics of Antimicrobial Peptides

Antimicrobial peptides (AMPs) constitute the innate host defense peptides found widely distributed among insects, fish, amphibians, and mammals including man. Thus, antimicrobial peptides (AMPs) serve as potent, broad-spectrum antibiotics found in many eukaryotic animal species [1,2]. Moreover, the AMPs demonstrate the potential to function as novel adjunct cancer therapeutic agents due to their ability to lyse and destabilize biomembranes, interact and/or form transmembrane channels, and engage in modulating host immunity against foreign invasive agents [3,4]. AMPs are known to act in concert with chemokine activities, ion channel interactions, histamine release, and the regulation of angiogenesis [4-6]. The objective of the present review is to provide evidence that AMPLs, such as growth inhibitory peptides, could serve as prime candidates to interact with cancer chemotherapeutic agents [7].

The AMPs can be produced from both synthetic and natural sources and these peptides demonstrate a broad-spectrum antimicrobial activity demonstrating both high targeting specificity and low toxicity. Furthermore, AMPs constitute part of the basic innate

immune systems of animals [8]. Mammals exhibit two major classes of AMPs termed: 1) cathelcidin and 2) defensins [9,10]. Cathelcidin (CTD) peptides have antibacterial, anti-tumor and anti-fungal properties (53) and are found in birds, chickens, and most mammals. However, humans have only one CTD termed LL-37 [11]. The second group of AMPs in mammals consist of the defensin peptides consisting of α, β, and γ subtypes, but only the α and β subtypes are present in humans. The α and β defensins are produced in cells such as neutrophils, leukocytes, macrophages, and epithelial cells present in the respiratory, digestive, and genitourinary systems; in addition, AMP are found in blood and urine [12].

The AMPs can be divided into five subgroups based on their net charge, protein/peptide origin, variable amino acid numbers and sequences, chemical modifications, and bioactivities [13]. The first subgroup is the anionic peptides; second is the cationic α-helical peptides; third is the cationic β sheet peptides; fourth is the extended cationic peptides; and fifth are fragments derived from various antimicrobial proteins.

Interestingly, the AMPL GIP-34 pregnancy peptide has most properties in common with the third subgroup, the cationic β-sheet peptides (see below), which are represented by the human defensin peptides. The defensin subgroup of peptides usually contain 2-8 cysteine residues forming one or more pairs of cysteines which can form disulfide bridges essential for structural stabilizations and biological functions. Such cationic peptides contain beta-hairpin loops, cyclized structures, hydrophobic amino acids, beta sheet structures, and an α-helical component [14-16].

B) The use of AMPL-peptides as Anticancer Agents:

Recent advances in the use of AMPs as anticancer agents may potentially offer alternative treatment options for patients undergoing chemotherapy. The AMPs have also been shown to provide novel means to increase targeted tumor cell effectiveness, lower expensive drug costs, and prevent development of drug resistance [5]. Bioinformatic technologies have further been

Table 1: Cell penetrating, antimicrobial peptides, and AFP-derived GIP-34 peptides are compared according to their biochemical/biophysical properties.

Characteristics, Traits, Properties	Cell-penetrating Peptides (CPP)	Antimicrobial Peptides (AMP)	AFP-Derived Growth Inhibitory Peptide (GIP	References
1) Cell membrane penetration effects	Forms transient transmembrane pores, penetrates through cell bilayer membrane	Forms transmembrane pores and/or ion channels, reduces the cell membrane potential, aids inmembrane leakage	Interacts with cell membrane and with transmembrane ion calcium channels	2-4
2) cell method internalization	a) Promotes energy dependent clathrin/caveolae endocytosis. b) energy-independent electrostatic interaction	Transmembrane channel passage, channel non-receptor intake similar to defensins	Interacts with membrane channels, disulfide non-receptor mechanism of cell uptake, pore and channel formation	6,10,12
3) Cell-specific targeting	Bacterial cell wall and virus coats, plasma membranes of vertebrates, Guanidinium group interaction	Microbial cell membrane, plasma membrane of vertebrate (mammals), transformed cancer cells	Plasma bilayer negative cell membrane; transformed cancer cells, stem cells, and bacterial membranes	19
4) Cell cargo delivery vehicles	Transports and carries conjugated and/or bound drugs, chemicals, and chemotherapeutic drugs to cells	Mostly small cargo delivery capability, binds metals, fuses with other peptides and proteins	Transmembrane passage of small ligands, binds dyes, metals, and promotes protein/peptide fusion	21
5) Cell toxicity	Cytophilic, Cytotoxic	Cytostatic and/or cytolytic	Cytostatic only	21
6) Amino acid (AA) composition	Excess of polycationic AA, some polar/non-polar and hydrophobic AAs	Largely amphipathic-containing both positive and negative charged AAs and hydrophobic AAs	Amphipathic forms containing positive and negatively charged, and hydrophobic AAs	23,24
7) Number of AAs in length	6-10 AAs	12-50 AA	8-34 AAs	15,16
8) Peptide secondary structure	Disordered in free solution, mostly lacking secondary structure	Displays alpha-helix, beta sheets, beta hairpin loop structures	Displays alpha-helix, Beta sheets, β-hairpin loops, and disordered structures	16
9) Effect of host immunity	Indirect effects on immune response, aids in innate immunity of the host	Promotes and enhances the innate immune response of host organism, initiates immunomodulation	Suppresses T-cell immune response and serves as MHC antigens for HLA-1 receptors; suppresses cytokine production	25
10) Angiogenesis effects	No effect on blood vessels formation	Modulates angiogenesis	Blocks/inhibits angiogenesis	26
11) Cytokine/chemokines effects	No effect on immune system cytokines	induces cytokine/chemokine production pro-inflammatory	Synergistic and regulate chemokine activities	8

AA=amino acids, GIP=Growth Inhibitory Peptide.

employed to modify, synthesize, and recombine existing AMPs for transition into anticancer agents [17,18]. Such transitional AMP peptides have been shown to display high cell penetrating activities, low toxicity, reduced number of side effects, and increased effective target specificity [19,20]. Furthermore, AMPs have now been reported to affect both solid tumors (pancreatic adenocarcinomas) as well as circulating leukemic cells [21,22].

C) The Amphipathic Traits of the AMPs:

The amino acid composition and structure of AMPs distinguish them from the pore-forming/cell-penetrating peptides (CPPs), which comprise short length peptides of 5-10 amino acids [10,11] (Table 1). In contrast, the AMPs may consist of 10-50 amino acids (AAs) and contain two or more cationic AAs, a large proportion of hydrophobic AAs, and contain some anionic AAs (53). The AMPs further contain many dipolar ions (Zwitterions) and constitute amphipathic traits including secondary structures of; 1) alpha-helices, 2) beta strands, 3) beta-hairpin loops, and 4) one or more disulfide bonds [2]. The amphipathicity of these peptides allow them to partition and/or permeabilize into the cell membrane bilayer and forming and/or interacting with transmembrane channels through electrostatic attraction [24]. It is of interest that the plasma bilayer cell membrane represents the prime target of the AMPs. Following cell internalization, such peptides can further interact and/or interfere with a) DNA, RNA, and protein synthesis, b) protein folding, c) signal transduction, d) cell membrane synthesis, and e) certain enzyme activators [25,26]. It is of interest that all the above properties of AMPL properties can be found in the AMPL-GIP described below (Table 1).

Understanding the Origin of the Pregnancy Alpha-Fetoprotein (AFP) Polypeptide as a Source of an Antimicrobial-Like Peptide

Alpha-fetoprotein (AFP) is a type of pregnancy associated oncofetal protein produced initially by the fetal liver, yolk sac, and gastrointestinal tract in microgram amounts during fetal development. In adults, however, AFP levels are present only in nanogram concentration; moreover, AFP levels in adults can become increasingly elevated in disorders which encompass both liver hepatomas and germ cell tumors. In adults, AFP has been utilized as a biomarker for these malignant conditions, can aid in early cancer diagnosis, and be employed to monitor treatment responses in both malignant and benign growth disorders [27,28].

B) Discovery of a Pregnancy AFP-derived Antimicrobial-like Growth Inhibitory Peptide (GIP)

As previously mentioned, GIP-34 is an AMP-like peptide, derived from the alpha-fetoprotein molecule. GIP was first discovered and developed by Mizejewski and his associates [29-31]. The significance of this fetal peptide, similar to defensin, lies in its unique biological properties found in several human disorders and in its potential therapeutic applications for cancer [32]. Previous GIP-34 studies have indeed demonstrated an ability of GIP to inhibit the growth of multiple cancer cells making it a potential candidate for various cancer treatment modalities [31,32].

The basic research to uncover the GIP-34 site imbedded in the pregnancy AFP molecule originated from multiple studies concerning the multifaceted roles exhibited by the AFP polypeptide. Following extensive research and experimentation, the specific peptide AA sequence fragment on AFP was isolated from a segment of 34 amino acids found within the 601 amino acid polypeptide chain of full-length AFP; this short peptide fragment was later shown to display inhibitory effects on cancer (unregulated) cell growth and subsequent cell proliferation [33,34]. Such observations proved to be noteworthy, especially since the AFP molecule itself was a growth enhancing protein, in contrast to the growth inhibiting properties displayed by the GIP peptide fragment. It was then realized that the research findings concerning GIP-34 could potentially present new insights into how similar protein-derived peptides could be harnessed for medical treatments and therapies in the future.

Potential Applications of the AMP-like GIP-34

The discovery of GIP-34 peptide opened up a myriad of potential applications, particularly concerning malignant and benign dysregulated and unwanted growths. Listed below are some of the key areas of research where GIP-34 could potentially contribute to making a significant impact in human biomedical and clinical settings.

1. ****Cancer Treatment**:** The ability of GIP to inhibit cancer cell growth presents novel avenues for development of targeted cancer therapies. By integrating GIP into adjunct treatment regimens, it might be possible to enhance the efficacy of existing chemotherapeutic treatments to improve cell targeting, minimize side effects, and reduce toxic drug effects in cancer patients [35,36].
2. ****Biomarker Development**:** GIP-34 could further serve as a biomarker for certain pregnancy fetal distress disorders possibly by providing a means for early prenatal detection and monitoring of dysregulated perinatal growth disorders [35]. Such events and factors might improve patient outcomes by enabling and enacting more timely and precisely-timed interventions in both pregnancy and adult dysregulated growth disorders, both malignant and benign [37,38].
3. ****Research and Drug Development**:** The discovery and usage of the AMPL-GIP could predictably spur further research into discovering similar AMPL peptides and their potential applications. Such studies might possibly lead to the development of new drugs and therapies to extend over a wide range of biological health conditions above and beyond cancer and dysregulated growth disorders.
4. ****Understanding Disease Mechanisms**:** Studying AMPL-GIP and its interactions with cancer and its associated dysregulated cells might further deepen our understanding of the mechanisms underlying carcinogenesis, cancer growth and progression, metastatic spread/migration, and cell adhesion and attachment. Such insights could possibly show promise in for developing more effective therapeutic drugs and treatments for various human disorders.

What is the Nature of the AMPL-GIP Peptide?

GIP-34 is a naturally occurring fetal peptide that has been studied by the National Cancer Institute and other research institutions for its potential to regulate cancer growth and promote overall human bodily health and well-being [34,35]. Such studies have involved both *in vitro* cell cultures in addition to *in vivo* animal studies. Overall, the AMPL-GIP has a peptide-based formula, is naturally derived, and can be presently non-prescription based.

The Traits and Properteis of Alpha-fetoprotein and its Derived AMPL- GIP

A. Since GIP-34 is a pregnancy derived peptide found only in the developing fetus, its production and presence ceases after birth. Thus, GIP is never present or produced anywhere in the human body other than during fetal development. However, a residual amount of newborn AFP (not GIP) remains after birth, but neonatal AFP microgram levels gradually decline to nanogram concentrations over a 9-month period following birth [39].

B. In contrast to GIP, the AFP full-length protein itself has unique properties that aid and provide rapid growth for the developing fetus; concomitantly, AFP monitors developing cells for normal growth and well-being of the fetus/newborn. Rogue or dysfunctional cells, such as cells in birth defective tissues, exhibit a negative net charge on their cell surface membranes while normal (non-malignant) fetal perinatal and newborn cells display a positive charge [40,41]. Even though GIP is hidden (concealed) within the molecular folds of the full-length AFP molecule, the AFP polypeptide itself has a sensitive "hot spot" stretch of amino acids near the middle portion of the 70 kD AFP molecule. This "activation sensitive hot spot", upon proper stimulation can induce a conformational change in the AFP molecule that exposes and reveals the GIP-34 amino acid peptide segment. The AFP-unveiled GIP, following its exposure on the AFP molecule, functions to prevent the growth and replication of unregulated and dysfunctional development of fetal and perinatal cells [42]. Thus, GIP is attracted to and only homes onto dysfunctional and growth dysregulated cells having a net cell surface negative charge on their cel surface membranes, in contrast to the positive net surface charge observed on normal developing cells [40].

C. Mizejewski et al. [30,31] observed that since all cancer cells, as well as rogue and non-growth regulated cells display a net negative cell membrane charge, such cells could be solely targeted for inhibition of further cell growth and proliferation [34]. Mizejewski et al. [39,40] have invested nearly 4 decades of research into GIP research having tested this peptide as a potential candidate for inhibiting growth of cancer and benign cells and potentially cells of other human disorders.

D. Solid cancer cell populations are composed of both tumor cell (98%) and stem cells (2%); and both cell types divide, replicate, and proliferate in the course of multiple mitotic cell divisions [43,44]. However, neither chemotherapy nor radiation treatment has the ability to destroy stem cells when standardized chemotherapeutic treatment protocols are applied. Even after a patient is declared "cancer-free," following multiple treatment regimens, it is still possible that the cancer could return many years later. This is because cancer stem cells are not destroyed and are very slow growing; thus, the stem cells could remain for many years to form, develop, and transition into actual cancer cells. This transition of stem cells into full-fledged tumor cells could then lead to cancer recurrence in many patients [45,46].

Cancer Cell Growth Inhibition by the AMPL GIP Utilized in both "*In Vitro*" and "*In Vivo*" Studies

A) Mechanisms of Action:

The mechanism of action of GIP-34 has been reported to involve blocking of cell signaling transduction cascades that can result in: 1) cell cycle S/G2 phase arrest, 2) prevention of cell cycle inhibitor (KIP/CIP) degradation, 3) protection of p53 from inactivation from phosphorylation, and 4) blockage of K^+ ion channels opened by estradiol and epidermal growth factors [32]. The disruption by GIP-34 action on cell surface activities can initiate tumor cell attachment, adhesion, cell pseudopodial extensions, platelet aggregation, and cell agglutination which significantly affects cancer cells. Thus, GIP can disturb, impair, and disable the ability of tumor cells to transduce signals, spread, adhere, and metastasize [35,38]. It is for the above reasons that GIP-34 has been described as a cell membrane disruptive agent in multiple cell signal transduction activities.

B) Cell Culture Studies of Cancer Cell Growth Inhibition:

United States governmental studies conducted by the National Cancer Institute (NCI) have documented that GIP-34 was indeed a cancer cell growth inhibiting agent. Inhibition of cancer growth was reported in 38 of 60 different cancer cell cultured lines. Such cancers included breast, prostate ovarian, central nervous system cancers, melanoma, kidney, lung, and colon [34]. Regarding breast cancers, the growth suppression in multiple cultured human breast cancers was shown to include cell lines such as MCF-7, T-47D, and BT-547. Additional studies further included *in vivo* Sarcoma 6WI-1 isografts *in vivo* assays in the mouse 6WI-1 model which were also performed (Table 2).

Table 2: Summary of an *in vitro* cytostatic assay using GIP in sulforhodamine-β stained cells in a 6-day culture assay.*

Human Tissue of Origin	Cell Line Code Designation	Percent (%) Growth Suppression
1. Colon	HCC-299	80
2. Ovary	OVCAR-4	85
3. Breast	MCF-7	80
4. Prostate	DU-145	90
5. Lung (non-small cell)	NCI-H460	80
6. Melanoma	UACC-257	75-80
7. Central Nervous System	SF-295	80
8. Kidney	TK-10	85
9. White Blood Cell	K-562	45

** Summarized data was extracted and polled from Reference 34 and performed by the National Cancer Institute, Bethesda, MD. GIP= Growth Inhibitory Peptide.

In further studies employing *in vivo* hollow fiber assays, the

National Cancer Institute Therapeutics Group reported that GIP-34 achieved growth suppressions up to 45% while demonstrating its greatest inhibition against ovarian cancers. These *in vivo* assays demonstrated that GIP-34 not only permeated through the hollow fiber pores themselves but suppressed growth in the tumor cells which had egressed to within the body cavity of the host mice [42].

AMPL-GIP was Found to be Effective against Cancer in Three Possible Modes

a. GIP can initially serve as a cancer preventative to inhibit initial cancer growth by means of inhibiting mitotic cell division in small clusters of cancer cell foci.
b. GIP is capable of can attacking negatively charged cancer and stem cells, thus preventing cancer regrowth many years later. Thus, GIP is able to attack both cancer and cancer stem cells thus preventing stem cell-to-cancer cell transitions later in life [53].
c. GIP also has the capability to override the cell's function of strictly regulating the amount of calcium taken up via ion channels into the cytoplasm of cancer cells [47,48]. Although calcium ions are essential for all body cells to exist, dysregulated and unrestricted amounts of calcium accumulation in cells can cause cell death [49].

Summary of the AMPL-GIP Discovery and Findings

- **GIP-34 Discovery:** GIP-34 is present as a novel AMPL-peptide derived from an unfolded molecular form of the alpha-fetoprotein molecule; this peptide is capable of preventing abnormal cell growth and blocking further cell proliferation and metastasis.
- **Medical Impact:** Application of novel studies with GIP could potentially open new therapeutic pathways and modalities to treat health disorders such as cancer, benign tumors, and in dysregulated cell growths.
- **Research Significance:** In the future, such studies with GIP might be capable of enhancing our understanding of malignant disease mechanisms that could pave the way for innovative therapies possibly by adjunct peptide treatments to accompany chemotherapies regimens.

Conclusions

The reported biological activities of antimicrobial-like GIP-34 could represent a potential advancement for applications in biomedical research including chemotherapy and associated cancer treatments. The AFP-derived GIP peptide possesses the potential for advancing adjunct cancer treatments and providing new therapeutic options for malignant and benign growths. As research with GIP advances, such studies could possibly unlock new opportunities and provide a means for new and innovative therapeutic strategies. The present studies lend credence to the power of persistent scientific inquiry and the ability to develop new approaches to some of the more challenging health issues of our present age.

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